UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)(KMW)**

PLAINTIFFS' REPLY BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT GEORGE E. JOHNSON, Ph.D.

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ARGUMENT

POINT I: DEFENSE EXPERT GEORGE JOHNSON'S "NOVEL" METHOD TO DETERMINE HIS "PERMITTED DAILY EXPOSURE" LEVEL FOR A CLASS 1 GENOTOXIC CARCINOGEN IS NOT RELIABLE.

Defendants' opposition continually references that the benchmark dose methodology used by defense expert Johnson is "approved" by the FDA. This is misleading. Dr. Johnson's benchmark dose (BMD) method is NOT used by any drug regulatory or scientific authority for CLASS 1 GENOTOXIC CARCINOGENS, such as NDMA and NDEA. The FDA's, EMA's and other regulatory bodies' acceptable daily intake (ADI) calculation method **is the accepted methodology** used to calculate daily NDMA and NDEA ingestion limits. In contrast, Dr. Johnson's own methodology for calculating daily ingestion limits of NDMA and NDEA is not. That is why the FDA's acceptable daily limit for NDMA is 96 nanograms and for NDEA is 26.5 nanograms while Dr. Johnson based upon his own calculation method advocates permissible daily intake levels of 6,200-21,4000 nanograms for NDMA, and 2,220-9,200 nanograms for NDEA. Plaintiffs are not arguing that benchmark dose methodology (BMD) is unknown or unrecognized for all chemicals just that it is not an accepted methodology for determining permissible daily exposures to NDMA or NDEA. The terms "acceptable daily intake" used by the FDA or "permissible daily exposure" used by Dr. Johnson are referring to the same concept – what is the daily limit of NDMA or NDEA that does not pose an unacceptable risk to patients. The FDA has stated that "[d]rug products that contain NDMA or NDEA above the limits in the table below pose an unacceptable risk to patients." https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan, Update 12/19/2018. The table shows the FDA's acceptable limit for NDMA is 96 nanograms per day, and 26.5 nanograms per day for NDEA. Id.

Under *Daubert,* Fed. R. Evid. 702 and 3rd Circuit law, the Courts evaluate the reliability of an expert's methodology by consideration of several key factors, including: whether a method consists of a testable hypothesis; the existence and maintenance of standards controlling the technique's operation; whether the method is generally accepted and the relationship of the technique to the methods which have been established to be reliable. *In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices & Prods. Litig.,* 509 F. Supp. 3d 116 at 131-132 (D. N. J., 2020), citing *United States v. Downing*, 753 F. 2d 1224, 1238-39 (3d Cir., 1985). Notably, "an expert's conclusions and methodology are not entirely distinct from one another." *General Electric v. Joiner*, 522 U.S. 136, 146 (1997).

Dr. Johnson's methodology fails each of these factors. His BMD method is not used for Class 1 genotoxin carcinogens including NDMA/NDEA by the FDA or the EMA. There are no uniform, or testable standards or agreed methodologies to apply the benchmark dose method to Class 1 genotoxins such as NDMA and NDEA and for that reason, BMD has not been accepted for these agents in the scientific community. When Defendants argue that Dr. Johnson is in the "forefront" of this methodology, they underscore that it is a new and developing technique, which may have application for some agents, but not for NDMA or NDEA. Defendants cannot point to any supporting authority that uses BMD for NDMA or NDEA except Dr. Johnson's own paper published May 2021, **AFTER** he was retained in this litigation. This is hardly a solid basis for arguing scientific acceptance. *Soldo v. Sandoz Pharms. Corp.,* 244 F. Supp. 2d 434, 527(W.D. Pa., 2003) (Expert opinions generated due to litigation have less credibility than those generated in academic research or other forms of "pure" research.)

As the FDA specifically stated in its publication, "Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry"; February 2021:

"**APPENDIX B. FDA DETERMINATION OF ACCEPTABLE INTAKE LIMITS**

> Identification of the acceptable intake (AI) values listed in section III of this guidance follows the procedures recommended in the ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018). A compound-specific AI can be calculated based on rodent carcinogenicity potency data such as TD_{50} values (doses giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2) identified in the public literature. Linear extrapolation to a probability of 1 in 100,000 (i.e., the accepted lifetime risk level used) is achieved by simply dividing the TD_{50} by 50,000. The AI (in mg/kg/day units) can then be converted to mg/day by multiplying by the human body weight (50 kg is the assumed body weight identified in the referenced guidance). **Linear extrapolation from a TD_{50} value is considered appropriate to derive an AI for M7 Class 1 impurities (known mutagenic carcinogens) with no established threshold mechanism".** (emphasis added).

The FDA then states how the daily accepted limit should be calculated using the accepted linear extrapolation methodology and, in fact, **uses NDMA** as the example stating:

> A summary of the AI derivation for NDMA is provided as an example. NDMA was identified as a mutagenic carcinogen in several species and is listed as a probable human carcinogen by the Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) program. TD_{50} values for NDMA are 0.0959 mg/kg/day (rat, based on Peto et al.) and 0.189 mg/kg/day (mouse) according to the CPDB. For the AI calculation, the lower (more conservative) value of the rat is used. The resulting AI associated with a 1 in 100,000 cancer risk over 70 years of exposure is calculated by dividing the TD_{50} by 50,000 and then multiplying by 50 to account for a patient with a 50-kg body weight, resulting in 0.0000959 mg/day NDMA, or approximately 96 ng/day NDMA. Ex. D, Appendix B.

It is abundantly clear that the linear extrapolation method is the accepted method for determining the safe daily intake of genotoxins like NDMA and NDEA.

In its earlier publication, *ICH Guidance for Industry M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (March 2018), the FDA explains why the TD_{50} linear extrapolation method is required for N-nitroso compounds like NDMA and NDEA:

> "Some structural groups were identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group of high potency mutagenic carcinogens, referred to as the *cohort of concern*,

comprises aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds". (note: TTC is defined in this document as the Threshold of Toxicological Concern). Ex. E, p. 5.

In this 2018 Guidance, the FDA speaks to the benchmark dose method, but not for use with NDMA and NDEA. However, even when discussing the benchmark dose method for other carcinogens, the FDA states that it is to be used with linear extrapolation. Ex. E, pp. 22-23. Dr. Johnson did **not** use linear extrapolation as part of his "method" and therefore is not even following the FDA's benchmark dose requirement for other carcinogens. Even the European Medicines Agency (EMA) in its Assessment Report on Nitrosamine impurities found that the Benchmark Dose method (BMDL10) (used by Dr. Johnson) was not ready for acceptance, as follows:

"The use of BMDL10 as point of departure instead of TD50 was extensively discussed by the CHMP in the Art 31 referral on sartans and the conclusion to use TD50 remains unchanged for the moment as there is still no internationally agreed methodology and the need for extensive multiple dose groups studies is much more essential for BMDL10 as for the TD50 approach. The ad-hoc meeting group acknowledged that a harmonized global approach is needed before the BMDL10 approach can be used." Ex. L, p. 44.

POINT II: DEFENSE EXPERT JOHNSON'S SOLITARY RELIANCE ON HIS OWN STUDY APPLYING HIS METHOD TO NDMA AND NDEA IS INSUFFICIENT TO ESTABLISH A RELIABLE METHODOLOGY.

Dr. Johnson can only cite to his own study, Ex. H., Johnson, et.al, *Permitted daily exposure limits for noteworthy N-nitrosamines*, May 2021 as support for using his PDE method to calculate safe limits of NDMA/NDEA. Ex. C, p. 60.

This one study must be critically evaluated by the Court on this Daubert motion. First, it was published after Dr. Johnson was retained by Defendants (Ex. B, pp. 141-145) who manufactured drugs contaminated with NDMA and NDEA that would directly benefit by his calculation of permissible daily exposure levels far in excess of the levels set by regulatory authorities. Second, the contributors to the paper comprise a list of "who's who" of

pharmaceutical company employees and pharmaceutical industry experts. Ex. H, p 293. For example, one of the authors of this solitary paper is Bhaskar Gollapudi, who lists his employer as "Exponent Consulting". Ex. H, p. 293. Exponent Consulting is a company offering defense experts for hire in litigation matters and has long served the pharmaceutical industry. Ex. B, pp. 237-241. Third, Dr. Johnson's paper was published in the journal of Environmental and Molecular Mutagenesis where Bhaskar Gollapudi serves as the editor-in-chief of the journal and Dr. Johnson is on the editorial board.[1] Aside from these issues, this single paper cannot serve as a basis for admissibility of his novel methodology, which leaves Dr. Johnson without any foundational support for reliability of his expert report findings. "…a court may well cast a jaundiced eye upon a technique which is not supported by any evidence of general acceptance…", *In re TMI Litig*., 193 F. 3d 613, 669 (3rd Cir., 1999)

POINT III: PLAINTIFFS HAVE PRESENTED PROOF OF THE CUMULATIVE DOSES OF NDMA AND NDEA THAT ARE ASSOCIATED WITH STATISTICALLY SIGNIFICANT INCREASED RISKS OF SPECIFIC CANCERS IN SUPPORT OF GENERAL CAUSATION.

The Defendants' argument that Plaintiffs are attempting to establish general causation by only showing the Defendants' valsartan containing drugs had levels above the FDA's permissible AI of NDMA and NDEA ignores the mountain of proof presented by the Plaintiffs in this case. Plaintiffs presented experts who evaluated the cumulative exposures to NDMA and NDEA that are associated with increased risks of cancer. For example, Plaintiffs' expert Dr. Dipak Panigrahy examined the totality of scientific evidence and supported his general causation opinions with peer reviewed human epidemiology studies that quantified NDMA exposure, found dose-response, and **statistically significant increased risks** of specific cancers associated

[1] Ex. II: Environmental and Molecular Mutagenesis Editorial Board, 2020

with certain lifetime cumulative exposures (LCEs). [2] These calculations were based on human dietary and occupational studies and allow for a calculation of lifetime cumulative exposures to show statistically significant increased risk of cancer, not FDA AI limits. The LCE approach is a scientifically accepted method for proving the doses associated with increased risk of disease which has been routinely accepted by the Courts. *Berman v. Mobil Shipping & Transp. Co.,* 2019 WL 1510941 [3]; *Gorton v. Air & Liquid Sys. Co*. 2020 WL 4193649 [4] and *Hoffeditz v. AM Gen., LLC*, 2017 WL 3332263 (D.N.J. 2017). [5] Plaintiffs also presented an expert report and testimony from Dr. Madigan that established LCE's associated with statistically significant increased risk of certain cancers based on the published peer-reviewed literature. [6] Plaintiffs demonstrated via Dr. Panigrahy's and Dr. Madigan's expert analysis that it was feasible for plaintiffs taking contaminated valsartan drugs to easily exceed LCE doses during the time the contaminated drugs were sold. [6,7].

Notably and in contrast, the human diet and occupational studies were disregarded by Dr. Johnson since this data does not fit into his theory and he decided to use only animal data. Ex. J, pp. 425-430; Ex. C., p. 58. The Plaintiffs in this MDL were exposed to much more than "trace" exposure, and those levels can reach and exceed the levels of exposure studied in the dietary and occupational studies that cause a statistically significant increased risk of cancer. These human

[2] Ex. DD: Plaintiffs' Rule 26 Expert Report of Dipak Panigrahy, MD and Addendum, pp.12, 86-91, 195
[3] Ex. EE: *Berman v. Mobil Shipping & Transp. Co*., 2019 WL 1510941; 2019 U.S. Dist. LEXIS 55671 (2019).
[4] Ex. FF: *Gorton v. Air & Liquid Sys.Corp*., 2020 WL 4193649; 2020 U.S. Dist.. LEXIS 129606 (M.D. Pa. 2020).
[5] Ex. GG: *Hoffeditz v. AM Gen, LLC*, 2017 U.S. Dist. LEXIS 123493; 2017 WL 3332263 (D.N.J., 2017).
[6] Ex. HH: Plaintiffs' Rule 26 Expert Report of David Madigan, Ph.D., p. 7
[7] Ex. DD: Plaintiffs' Rule 26 Expert Report of Dipak Panigrahy, MD and Addendum, pp. 88-90

studies provide scientific data that once LCE exceeds the levels in the 2nd and above quartiles, tertiles and quintiles, that risk of cancer is increased to a statistically significant degree. This is all that is required for general causation. *In re Roundup Prods. Liab. Litig.,* 390 F. Supp. 3d 1102, 1113 (N.D. Ca. 2018) ("…the inquiry at the general causation phase is not whether glyphosate gave NHL to any of the particular plaintiffs who brought these lawsuits, and the plaintiffs need not establish any particular level of exposure. It's enough in this litigation, at this stage, for the plaintiffs to show that glyphosate can cause NHL when people are exposed to the highest dose people might plausibly experience.")

Dr. Johnson's methodology is inadequate due to his arbitrary exclusion of this highly relevant category of scientific evidence.

Contrary to Defendants' assertions, Plaintiffs' analysis of lifetime cumulative dose exposure does not ignore endogenous formation of NDMA/NDEA or nitrosamines from other sources. Quite to the contrary, the additional levels of NDMA in valsartan contaminated drugs taken by Plaintiffs is ADDITIVE to their existing diet or other NDMA exposures. So, the lifetime cumulative exposure risk of cancer is increased when the exogenous NDMA/NDEA intake from years of taking contaminated valsartan is added. That is why the human diet and occupational studies (which include background cancer rates in the 1st quartile, 1st tertile or 1st quintile) is scientifically sound as a basis to ascertain levels of exposure that lead to increased risk of various cancers.

POINT IV: THE PETO STUDY IS ACCEPTED AS THE MOST SIGNIFICANT SCIENTIFIC STUDY ON N-NITROSAMINE DOSE RESPONSE.

Dr. Johnson primarily relied on the Peto study, *Effects on 4080 Rats of Chronic Ingestion of N-Nitrosodiethylamine or N-Nitrosodimethylamine: A Detailed Dose-Response Study*, Cancer Research, 1991. Ex. F. Defendants suggest the Peto study doesn't support that low dose rates

(under 1 ppm) had a linear relationship with no indication of any threshold (Ex. F, p. 6415) but ignore that the FDA found it persuasive and used this Peto study to determine the TD_{50} values for NDMA/NDEA. Ex. D., Appendix B, p. 1. Defendants also ignore the Peto study's plain language which specifically states that NDMA and NDEA have "no indication of any threshold." Ex. F, p. 6415. Notably, coming to conclusions the authors of the study do not make" demonstrates a "lack of scientific rigor." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1248 (11th Cir. 2005); *see also In re Nexium Esomeprazole*, 662 F. App'x 528, 530 (9th Cir. 2016).

Interestingly, Defendants also cite to the FDA Nitrosamine Workshop -Report Final (July 20, 2021). D's Ex. B. This FDA Workshop Report demonstrates the unreliability of many of Dr. Johnson's opinions. For example, the Report states that NDMA/ NDEA are rapidly metabolized in the body and that there are significant questions about whether and to what extent these substances may be formed endogenously. The report states, "no quantitative assessment of NDMA or NDEA is available because of their rapid metabolism" and "only rough estimates are available in the literature on endogenous formation of NDMA" due to its rapid metabolism. This same workshop report states: "Currently, it is unknown if endogenous formation of carcinogenic nitrosamines exceeds, equals or is less than the levels in drugs." D's Ex. B, p. 25. This is contrary to Dr. Johnson's assertions that levels of endogenous formation are higher than the levels in the FDA test results, so this issue remains an unknown factor unfortunately for Dr. Johnson as it is not a reliable foundation for his opinion as required by *Daubert v. Merrell Dow Pharms, Inc.*, 509 US 579, 584-587 (1995).

The FDA Workshop Report also confirms that "Nitrosamines are one of the few chemicals in the Cohort of Concern (CoC)…a class of highly potent mutagenic carcinogens that requires strict controls to limit their amounts." D's Ex. B, p. 3. The Workshop states that due to their potency, nitrosamines were extensively studied in the 1960s with over 300 nitrosamines

tested in rodent cancer bioassays and over 90% were found to be carcinogenic and that they caused tumors in various organs including, liver, lung, nasal cavity, esophagus, pancreas, stomach, urinary bladder, colon, kidneys, and central nervous system. D's Ex. B, p. 3. The FDA Workshop Report confirmed that the BMDL approach lacked adequate data to use this method and that the TD_{50} approach is "the best-available carcinogenic risk estimation." D's Ex. B, p. 8. All of this underscores that linear extrapolation TD_{50} is the methodology accepted in the scientific community for establishing daily permissible intake limits of NDMA and NDEA.

POINT V: DR. JOHNSON'S DELIBERATE DECISION TO DISREGARD THE VALSARTAN DRUG MANUFACTURERS' OWN NDMA/NDEA TESTING DATA WAS METHODOLOGICALLY UNSOUND.

Defendants offer no adequate rationale why Dr. Johnson did not apply his methodology to the actual test results OF THE DEFENDANTS, by whom he has been retained. No suggestion is made that these manufacturer test results are invalid or inaccurate in any way by Defendants. Indeed, it would be curious if the Defendants claimed their own test results did not accurately determine levels of NDMA/NDEA using the FDA's methodology. The only explanation for omitting the Defendants' test results by Dr. Johnson is because many results exceed (and many far exceed) the NDMA/NDEA levels in the few batches tested by the FDA. Dr. Johnson did not use the manufacturer's own test results because they would often exceed his PDE limits.

For example, ZHP/Solco reported NDMA test results [redacted] Ex. Q. This level far exceeds Dr. Johnson's NDMA PDE level of 6,200 nanograms per day (upper limit 10,700 nanograms) (50 kg patient) and 12,400 nanograms per day (upper limit 21,400 nanograms (100 kg patient). Another example of ignoring the Defendants' test results are the Torrent NDEA levels [redacted]

[redacted]. This level exceeds Dr. Johnson's NDEA PDE level of below 2,200 nanograms per day (upper limit 4.6) (50 kg patient) or 4,400 nanograms per day (100 kg patient). Ex. C, pp. 13-15.

This is the only logical explanation for why the manufacturers' test results were ignored. This is classic cherry-picking of select data to fit a pre-conceived litigation driven result without other scientific justification. Ex. B, p. 253 and Ex. J, p. 381.

This alone, is a basis for rejecting Dr. Johnson's opinions on PDE and cancer causation. This is more than simply cross-examination fodder or mere scientific dispute; it goes to the essence of reliability of Dr. Johnson's opinions in this proceeding. "An expert may not pick and choose from the scientific landscape and present the Court with what he believes the final picture looks like." *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004) (expert excluded by Court; ignoring available information vital to opinions is cause for preclusion). *Accord, In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 341 F. Supp. 3d 213, 242 (S.D.N.Y. 2018). See also*, In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig*., 26 F. Supp. 3d 449, 461-462 (E.D. Pa. 2014).

POINT VI: THE CASES CITED BY DEFENDANTS ARE INAPPLICABLE TO THE FACTS IN THIS CASE.

Defendants cite to cases dealing with dose exposure analysis and cite *McClain v. Metabolife, Inc*., 401 F. 3d 1233 (11th Cir., 2005); *In re Abilify (Aripiprazole) Prods. Liab. Litig*., 299 F. Supp. 3d 1291 (N.D. Fl. 2018) and *In re Bextra & Celebrex Mktg. Sales Practices & Prods. Liab. Litig*., 524 F. Supp. 2d 1166 (N.D. Cal. 2007). None of these cases involved a Class 1 genotoxic carcinogen such as NDMA and NDEA. *McClain* involved an herbal weight loss drug supplement alleged to cause strokes or cardiac injury; *Abilify* involved a side effect of uncontrolled impulsive behavior including gambling; *Bextra and Celebrex* were pain medications for arthritis causing heart attacks or strokes. Since a genotoxin by its definition

directly damages DNA in animals and people, they are very different agents than non-genotoxins and are regulated and evaluated differently.

The genotoxic damage to DNA by NDMA and NDEA with carcinogenic outcomes is an injury that would satisfy the burden of *McClain v. Metabolife, Int'l., Inc*., 401 F. 3d 1233, 1239 (11th. Cir., 2005) since the medical community recognizes the toxicity of these agents to cause cancer as alleged by Plaintiffs,

Defendants cite to cases that failure to meet regulatory standards is not proof of general causation by itself. As explained above, Plaintiffs are not relying solely on the FDA limits, and are not even using the FDA acceptable intake limits for their cumulative exposure analysis that supports statistically significant increased risks of cancer at cumulative amounts of NDMA and NDEA exposure that can be reached by patients taking contaminated valsartan containing drugs. As such, this argument is not relevant to Plaintiffs' theories.

CONCLUSION

For the reasons set forth in Plaintiffs' motion, Dr. George Johnson should be precluded from offering his opinions related to general causation.

Respectfully submitted,

Rosemarie Riddell Bogdan

CERTIFICATE OF SERVICE

I hereby certify that on January 6, 2022, I electronically filed the foregoing document with the Clerk of the Court using the CM/ECF system which will send notifications of such filing to the CM/ECF participants registered to receive service in this MDL.

/s/ Rosemarie Riddell Bogdan
Rosemarie Riddell Bogdan